IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 6770
ZAUDERER *et al.*	Art Unit: 1639
Appl. No. 09/987,456	Examiner: Epperson, J.D.
Filing date: November 14, 2001	Atty. Docket: 1821.0070004/EJH/T-M
For: ***In Vitro* Methods of Producing and Identifying Immunoglobulin Molecules in Eukaryotic Cells**	

Reply Brief Under 37 C.F.R. § 41.41

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PO Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants filed a Brief on Appeal to the Board of Patent Appeals and Interferences for the above-captioned application on April 27, 2007, appealing the decision of the Examiner in the Final Office Action mailed October 31, 2006. An Amended Brief on Appeal was filed on July 6, 2007. The Examiner's Answer was mailed on August 10, 2007. In reply to the Examiner's Answer, Appellants submit this Reply Brief under 37 C.F.R. § 41.41. In addition to responding to the Examiner's Answer, this Reply Brief also addresses cases relating to obviousness determinations that were decided since Appellants filed their Amended Brief on Appeal.

I. The Examiner's Assertions of a Reasonable Expectation of Success are Erroneous

The Examiner has maintained the erroneous conclusion that claims 84, 88-97, 99, 103, 107-122, and 129-131 would have been obvious because one of ordinary skill in the art would have had a reasonable expectation of success in combining Rowlands with Zauderer and Waterhouse ("the cited references"). *See* Examiners Answer at pages 24-31. In maintaining the obviousness rejection, the Examiner has mischaracterized and improperly disregarded the Declaration of Dr. Walter J. Storkus, and has impermissibly substituted his own opinion for that of an expert. The Examiner has not provided any reasonable or relevant countervailing evidence to contradict Dr. Storkus's opinion regarding the lack of a reasonable expectation of success or to support the Examiner's own conclusion that one of skill in the art would have had a reasonable expectation of success in combining the cited references. Accordingly, as discussed below and in Appellants' Brief of July 6, 2007, the Examiner has failed to establish a *prima facie* case of obviousness.

The U.S. Patent and Trademark Office must consider evidence provided in the form of expert declarations when making an obviousness determination. *See In re Sullivan*, No. 2006-1507 (Fed. Cir. Aug. 29, 2007). In *Sullivan*, the Federal Circuit recently vacated a decision by the Board that affirmed the examiner's obviousness rejection of claims to an antibody composition against snake venom. *Id.* The Federal Circuit reversed, concluding that the Board did not properly consider the three expert declarations that were submitted as rebuttal evidence against the obviousness rejection. *Id.* at 8. Furthermore, an examiner is not permitted to substitute his or her opinion for

that of an expert. *See In re Zeidler*, 682 F.2d 961, 966-67, 25 U.S.P.Q. 490 (C.C.P.A. 1982) (holding that the decision of the Board of Patent Appeals and Interferences constituted reversible error, "the board having erroneously substituted its judgment for that of an established expert in the art.").

Post-*KSR* decisions by the Federal Circuit clearly indicate that the requirement for showing a reasonable expectation of success still plays an important role in an obviousness determination and, further, that evidence demonstrating a lack of a reasonable expectation of success must be considered. *See, e.g., Takeda Chemical Industries, Ltd. v. Alphapharm PTY., LTD*, 492 F.3d 1350, 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007); *Forest Laboratories, Inc. v. IVAX Pharmaceuticals, Inc.*, No. 2007-1059, slip op. (Fed. Cir. Sept. 5, 2007). *Cf. PharmaStem Therapeutics Inc. v. ViaCell Inc.*, 491 F.2d 1342, 83 U.S.P.Q.2d 1289 (Fed. Cir. 2007). In each case where evidence supported a finding that one of ordinary skill in the art did not have a reasonable expectation of success, the claims at issue were deemed to be non-obvious. For example, in *Takeda*, the court determined that, even though a compound similar to the claimed anti-diabetic compound, piaglitazone, was known in the prior art, one of ordinary skill would not have had a reasonable expectation of success in obtaining the claimed invention. *Takeda*, 491 F.3d at 1360-62, U.S.P.Q.2d at 1177-78. The evidence showed that the prior art compound had undesirable side effects, but only two modifications were required to make the claimed compound from the prior art compound. *Id.* at 1360, U.S.P.Q.2d at 1177. Although the methods for making these modifications (*i.e.*, "homologation" and "ring-walking") were known in the art, the district court nevertheless concluded that the evidence favored a finding that one of ordinary skill in the art would not have had a

reasonable expectation that performing these modifications "would cause a compound to be more efficacious or less toxic." *Id.* at 1361, 83 U.S.P.Q.2d at 1177-78. Accordingly, the Federal Circuit affirmed the holding that the invention. *Id.* at 1362-63, 83 U.S.P.Q.2d at 1177.

Similarly, in *Forest Laboratories*, the Federal Circuit upheld a district court's finding that one of ordinary skill would not have had a reasonable expectation of success in attempting to separate a substantially pure enantiomer of citalopram. *Forest Labs.*, slip op. at 5. Even though the racemic mixture of citalopram was known in the prior art, the district court held that there was no reasonable expectation of success because there was evidence that others had tried unsuccessfully to resolve racemic citalopram, that one of the named inventors attempted the separation only as a last resort, and that one of ordinary skill in the art would have faced "a real possibility that the resolved intermediate would re-racemize during the attempt to convert it from the diol intermediate enantiomer to the desired citalopram enantiomer." *Id.* at 4-5, 9-11. The Federal Circuit, again, affirmed the district court's finding of non-obviousness. *Id.* at 11. Thus, where evidence showed the lack of a reasonable expectation of success in the art, there was no *prima facie* obviousness.

In both *Takeda* and *Forest Laboratories*, the claimed invention was deemed non-obvious based on evidence that the skilled artisan would have perceived major obstacles preventing a reasonable expectation of success. Such is the present case. Appellants' submitted evidence in the form of a Declaration by Dr. Walter J. Storkus. Dr. Storkus provided a factual basis for his opinion that there would have been no reasonable

expectation of success in obtaining the claimed invention. *See* Storkus Declaration (submitted as Exhibit 4 with Appellants' Brief of July 6, 2007). Dr. Storkus, an expert in immunology, explained the perceived obstacles to the claimed invention and why he did not believe that there would have been a reasonable expectation of success, even in view of the cited references. *See id.* As a member of the Scientific Advisory Board (SAB) of Vaccinex, Inc.[1], Dr. Storkus evaluated the claimed technology around the time the present application was filed, and therefore was able to provide an account of his thoughts about the invention *at that time*.

In particular, Dr. Storkus stated: 1) that he thought that it would not be practical to screen the number of eukaryotic cells necessary to find antigen-specific antibodies, as was possible via screening phage; and 2) because of the differences in the conditions of eukaryotic cytoplasm as compared to prokaryotic periplasm, he thought that random pairs of immunoglobulin heavy and light chains would fail to associate properly in eukaryotic cells and therefore would not allow selection of antigen-specific antibodies. *Id.* at paragraph 7. Dr. Storkus further explained that expressing a single antibody, as in Rowlands, is "far simpler" than expressing heavy and light chain pairs from separate libraries, because the Rowlands antibody had already been selected for heavy and light chains that paired correctly and efficiently to specifically bind antigen. *Id.* at paragraph 9. Dr. Storkus also stated that Zauderer does not address the concern of assembling heavy and light chains from two *separate* libraries in eukaryotic cells because only one library was introduced into host cells. *Id.* Therefore, Dr. Storkus concluded that his expectations would not have changed in view of these references. *Id.*

[1] Vaccinex, Inc., is the exclusive licensee of the present invention.

Hence, the limits on the ability to screen eukaryotic host cells as opposed to phage particles would have been considered an obstacle to the reasonable expectation of success in arriving at the claimed methods by combining Rowlands with Zauderer and Waterhouse. Also, the fact that immunoglobulin fragments were known to pair together when concentrated in the periplasmic space of a bacterium would not have predicted that separately expressed heavy and light chains from two random vaccinia virus libraries would find each other in the much larger environment of the eukaryotic cytoplasm and pair together with sufficient frequency to allow selection of antigen-specific immunoglobulins. Thus, analogous to *Takeda*, where one of ordinary skill in the art would not have reasonably expected the known chemical modifications to yield a suitable anti-diabetic compound from an unsuitable one, and analogous to *Forest Laboratories*, where the skilled artisan would not have reasonably expected successful separation of enantiomers from a known racemic mixture, Dr. Storkus, an expert in the field, provided clear factual reasons why there would not have been a reasonable expectation of success, even based on what was known about expressing individual antibodies and screening immunoglobulin libraries in prokaryotic systems.

In a recent case where the evidence submitted to show no reasonable expectation of success was found to be insufficient, the Federal Circuit found obviousness. *PharmaStem*, 491 F.3d 1342, 83 U.S.P.Q.2d 1289. In *PharmaStem,* claims to cryopreserved umbilical cord stem cells for reconstituting the human immune system were deemed to be obvious over the prior art. *Id. at* 1367, 83 U.S.P.Q.2d at 1307. Despite the submission of an expert declaration to the contrary, the court found that there was sufficient countervailing evidence to show a reasonable expectation that cord blood

contained hematopoietic stem cells. *Id.* at 1360-63, 83 U.S.P.Q.2d at 1302-04. In the declaration, the expert contended that, prior to the application at issue, there was no indication in the art that cord blood contained hematopoietic stem cells. *Id.* at 1361, 83 U.S.P.Q.2d at 1302-03. However, this was clearly contradicted not only by the prior art references, but also by the applicants' own statements in the specification that the prior art references provided strong evidence regarding the presence of hematopoietic stem cells in cord blood. *Id.* at 1361-62, 83 U.S.P.Q.2d at 1302-03. Thus, the Federal Circuit held that the prior art and the applicants' statements in the specification outweighed the expert's assertions that there was no reasonable expectation of success. *Id.* at 1362, 83 U.S.P.Q.2d at 1303-04.

The present case is clearly distinguishable from *PharmaStem* because there were no such admissions by the Appellants or any other evidence of record that contradict the statements of Dr. Storkus. While the Examiner's Answer asserts that Appellants' specification contains admissions regarding the prior art that allegedly support his arguments that there was a reasonable expectation of success, these arguments fall completely flat because the parts of the specification cited by the Examiner merely mention that of phage display libraries could be used to construct large libraries of immunoglobulins. S*ee* Examiner's Answer at 30. Appellants do not disagree that it was known that libraries of phage could be used to screen antibodies in prokaryotic host cells. But the Examiner's point is irrelevant because the cited passages *do not* state that the use of two expression libraries was known or expected to be successful for antibody selection in *eukaryotic cells*. Thus, unlike the patent at issue in *PharmaStem*, Appellant's specification does not make admissions that contradict Dr. Storkus's opinion that the

prokaryotic phage display literature was not instructive regarding how antibody selection would occur in *eukaryotic* cells, nor does it state or even imply that one of ordinary skill in the art would have had reasonable expectation of success in achieving the claimed invention.

Despite the factual basis of the Storkus Declaration, the Examiner has effectively disregarded Dr. Storkus's opinion without providing any relevant factual evidence of his own to show that there was a reasonable expectation of success. First, the Examiner continues to assert that the Storkus Declaration is "ambiguous" because "Dr. Storkus never states at 'what time' was the idea [for the invention] presented to him." Examiner's Answer at 28-29. Indeed, the Examiner engages in wild speculation about different scenarios of when Dr. Storkus might have first learned of the present invention. *Id.* at 29. However, Appellants maintain that it is quite clear that from the Storkus Declaration and from Appellants' Brief that Dr. Storkus was presented with the idea for the invention in his capacity as a member of the Vaccinex Scientific Advisory Board (SAB) and he evaluated the technology contemporaneously with the filing of the present application. *See* Exhibit 4 and Appellants' Brief of 7/6/2007 at 16. That is the purpose of a scientific advisory board: to review the technology and proposed research plans of an organization. Dr. Storkus's first-hand recollection of his thoughts about the invention provide an indication of the prevailing thought when the present application was filed. The Examiner's conjecture about hypothetical situations in which Dr. Storkus could have learned about the invention are unsupported by evidence and without merit.

In the Examiner's Answer, the Examiner further asserts that there would have been a reasonable expectation of success because the structure of an antibody protein was known and "there's no reason to expect 'less' pairing that [sic] would be formed from the use of two libraries because the changes made would not affect those parts of the antibody heavy and light chain that are responsible for the pairing." Examiner's Answer at 38-39. The Examiner also alleges that there would have been a reasonable expectation of success because the Zauderer reference "state[s] that they can 'efficiently' produce libraries and even tout 100% conversion using the tri-molecular approach." *Id.* at 29. However, neither of these arguments has any relevance to the expectation of success of the *claimed invention*.

With respect to the Examiner's first argument, the fact that antibody structure was known would not make it any more predictable whether immunoglobulin heavy chains and light chains that are randomly expressed from two separate libraries in a population of mammalian host cells would pair together in the eukaryotic environment with sufficient frequency to allow selection of polynucleotides encoding antigen-specific immunoglobulins. That issue is addressed in detail by the Storkus Declaration and in Appellants' Brief, as discussed above.

With respect to the Examiner's second argument that efficient pairing of heavy and light chains would be expected in view of statements from Appellants' specification and the Zauderer reference, Appellants submit that the excerpts cited by the Examiner are completely off point. The Examiner is relying on statements regarding the efficiency *with which vaccinia virus vector libraries can be constructed* to support the argument

that immunoglobulin heavy and light chains randomly expressed from the libraries *will pair together efficiently*. But these are completely separate considerations. The efficiency with which the libraries were constructed--that is, how the nucleic acid inserts were put into the vectors--provides no guidance as to how the immunoglobulin heavy and light chain polypeptides would behave (*e.g.*, pair together) once the libraries of vectors are introduced into a population of mammalian host cells and expressed. Therefore, the Examiner's Answer has not provided any relevant evidence or arguments to contradict the Storkus Declaration or show that one of ordinary skill in the art would have had a reasonable expectation of success.

Even though Appellants have provided evidence that prokaryotic phage display would not have provided a reasonable expectation of success for using two libraries in a eukaryotic system, the Examiner continues to ignore this distinction. A similar situation was addressed by the Federal Circuit in *In re Vaeck*. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). In *Vaeck* the claimed invention was directed to a chimeric gene capable of being expressed in cyanobacteria cells, comprising a promoter region effective for expression of a DNA fragment in Cyanobacterium and at least one DNA fragment from a insecticidally active *Bacillus* bacterial gene. *Id.* at 489-90, 20 U.S.P.Q.2d at 1439-40 The Federal Circuit determined that there was no reasonable expectation of success in combining: 1) a reference that disclosed the expression in cyanobacteria of a chimeric gene comprising a chloroplast promoter sequence fused to a CAT selectable marker gene; and 2) three secondary references that collectively disclosed the expression of genes encoding certain *Bacillus* insecticidal genes in three different species of bacterial hosts, two of the genus *Bacillus* and *E. coli*. *Id.* at 493-94,

20 U.S.P.Q.2d at 1442-44. The court determined that "[t]he prior art simply does not disclose or suggest the expression in cyanobacteria of a chimeric gene encoding an insecticidally active protein, or convey to those of ordinary skill in the art a reasonable expectation of success in doing so. . . . The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria for unrelated purposes." *Id.* at 493, 20 U.S.P.Q.2d at 1443 (emphasis added). In making their determination, the Federal Circuit stated that "it is only in recent years that the biology of cyanobacteria has been clarified .... Such evidence of recent uncertainty regarding the biology of cyanobacteria tends to rebut, rather than support, the PTO's position that one would consider the cyanobacteria effectively interchangeable with bacteria as hosts for expression of the claimed gene." *Id.* at 494, 20 U.S.P.Q.2d at 1443. As in *Vaeck*, the evidence in the present case indicates that one of ordinary skill in the art at the time of filing would not have had a reasonable expectation of success in merely interchanging a prokaryotic system of phage display with the eukaryotic system of the present invention. Without more than this bare assertion, the Examiner has not shown that there was a reasonable expectation of success in view of the Storkus Declaration.

Appellants also point out that the Examiner's arguments that the Storkus Declaration is not commensurate in scope with the claims are misplaced. *See, e.g.,* Examiner's Answer at 26-27. This is the standard used for rebutting a *prima facie* case of obviousness with a showing of unexpected results. *See e.g., In re Petersen*, 315 F.3d 1325, 1330-31, U.S.P.Q.2d 139, 1382-85 (Fed. Cir. 2003). In the present case, the Examiner has not even established a *prima facie* case of obviousness because, as

evidenced by the Storkus Declaration, there would have been no reasonable expectation of success. Furthermore, the Storkus Declaration *is* commensurate in scope with the claims. Dr. Storkus stated that he "thought specific antibodies of interest would occur at relatively low frequency and it would not be practical to screen the number of eukaryotic cells necessary in order to find an antibody that had specificity for a specific antigen of interest." Storkus Declaration at page 3. Furthermore, the fact that selection of antibody fragments had been performed in phage did not convince Dr. Storkus that eukaryotic cells could be used to screen for antigen-specific antibodies because of the limitations on screening throughput for eukaryotic cells compared to phage particles. Also, Dr. Storkus indicates that it was not clear, just because assembly of two separate immunoglobulin chain fragments in the periplasmic space of a prokaryotic cell could be achieved, that assembly in the cytoplasm of a eukaryotic cell would also occur to allow selection of polynucleotides encoding an antigen-specific immunoglobulin. *Id.* at pages 3-4.

The claims are directed to a method of selecting polynucleotides encoding an immunoglobulin heavy or light chain, which, as part of an immunoglobulin molecule, *is specific for an antigen.* If the immunoglobulin heavy and light chains are not capable of pairing together in the host cell--*e.g.*, if they do not "find" each other in the cytoplasm and assemble to form immunoglobulin molecules--then no antigen-specific immunoglobulin molecules could bind the antigen of interest or be detected as part of a specific antigen-antibody complex, and polynucleotides encoding the immunoglobulin subunit polypeptides could not be recovered according to the claimed method. This is completely commensurate in scope with the Storkus Declaration.

Since the Examiner has not provided any specific evidence or relevant scientific rationale to counter the statements of Dr. Storkus or otherwise show that one of ordinary skill in the art would have had a reasonable expectation of success, the Examiner has not established a *prima facie* case of obviousness.

II. The Examiner's Assessment of the Invention as "Mere Scale-up" is a Mischaracterization

Appellants have provided evidence that the claimed invention is more than a predictable result or "mere scale-up." In *KSR*, the Court emphasized that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 127 S.Ct. at 1739, 82 U.S.P.Q.2d at 1395. Post-*KSR* cases have adopted *KSR*'s "functional" approach to obviousness determinations. *See, e.g., Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 83 U.S.P.Q.2d 1687 (Fed. Cir. 2007) (obviousness finding based in part on lack of evidence that a reader component in a children's learning device was "uniquely challenging or difficult for one of ordinary skill in the art" or "represented an unobvious step over the prior art."); *Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, Nos. 2006-1530, -1555 slip op. (Fed. Cir. Sept. 11, 2007) (Claims to an stereoisomer of ramipril were found to be obvious because "there is no evidence that separating 5(S) and SSSR ramipril was outside the capability of an ordinary skilled artisan."); *Ex Parte Smith*, 83 U.S.P.Q.2d 1509 (Bd.Pat.App.&Int. 2007) (affirming obviousness rejection of a pocket insert in a bound book because there was no evidence that the invention yielded anything more than a "predictable result" of the prior art combination); and *Ex Parte Catan*, 83 U.S.P.Q.2d 1569, 1576 (Bd.Pat.App.&Int. 2007) (claims to a consumer

electronics device were obvious because "Appellant has presented no evidence that combining the Nakano device with the Harada bioauthentication means would have required anything more from one of ordinary skill in the art than to substitute one authentication means for a more advanced one.") The common thread in all of these cases is that the invention at issue was found to be obvious because there was no evidence that it represented an unobvious step over the prior art or was uniquely challenging or difficult to one of ordinary skill in the art.

The requirement to consider the claimed invention as a whole is a statutory mandate that remains unaffected by the Supreme Court's decision in *KSR*. *See* 35 U.S.C. § 103(a) ("A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that *the subject matter as a whole* would have been obvious at the time the invention was made . . . ." (emphasis added)).

In the Examiner's Answer, the Examiner asserts that the claimed invention would have been obvious because one of ordinary skill in the art would know from Rowlands how to express a antibody in a eukaryotic cell, and from Zauderer how to construct an expression library in vaccinia virus, and that, therefore, he would know how to make a library of antibodies. Examiner's Answer at 40-41. The Examiner then draws the erroneous conclusion that producing two libraries is merely a matter of "duplication" or "scale up." *Id.* at 41. This is a gross oversimplification and fails to consider the claimed invention as a whole. Even if one of ordinary skill in the art would know how to produce a library of immunoglobulin chains, or even two such libraries, he would not have

known that the two libraries could be introduced into a population of mammalian cells to select polynucleotides encoding antigen-specific immunoglobulins, as in Appellants' claimed invention. As discussed in the Storkus Declaration, it was thought that the throughput limits on screening eukaryotic cells would not permit selection of antigen-specific antibodies. Storkus Declaration at 3. Therefore, the Examiner's focus only on the construction of the libraries disregards the evidence in the Storkus Declaration that the present invention was not merely the predictable result achieved by combining old elements that were known in the art, and fails to consider the claimed invention as a whole.

In the present case, the Examiner did not properly consider the declaration evidence showing that the claimed invention is not merely a predictable result or a "scale up" of a known method. He also did not consider the claimed invention as a whole in making the rejection. Therefore the Examiner failed to establish a *prima facie* case of obviousness.

III. The Claims are not Unpatentable for Non-statutory Double Patenting

Although Appellants maintain that claims 84, 88-97, 99, 103, 107-122, and 129-131 are not unpatentable under the doctrine of non-statutory obviousness-type double patenting over claims 1-84 of U.S. Patent Application Serial No. 10/052,942 ("the '942 application"), in view of Rowlands, or over claims 46-128 of U.S. Patent Application Serial No. 10/465,808 ("the '808 application"), in view of Rowlands and Zauderer, Appellants respectfully maintain their request that these rejections be held in abeyance until the remaining issues outstanding in this application have been resolved.

IV. Conclusions

In light of the arguments above, as well as those set forth in Appellants' Brief on Appeal filed July 7, 2007, Appellants respectfully submit that the final rejections of claims 84, 88-97, 99, 103, 107-122, and 129-131 were improper and should be reversed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Tracy L. Muller
Attorney for Appellants
Registration No. 55,472

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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